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Re: European Patent Application No. 04763653.5

AFFIDAVIT

by dr. Fabio Rinaldi, Medical Doctor, specialised in dermatology.

I, Fabio Rinaldi, declare and state that:

- I am an expert in dermatology
- I am the author of many international dermatological publications
- I am the President of the International Hair Research Foundation (IHRF) and Member of Alliance of Hair Foundation in the USA
- I am a Professor at the Trichological Master held at the University of Florence
- I have read prior art documents D1 to D9 cited during the prosecution of the instant application.

I set forth my opinion as follows:

Normal healthy (or physiological) skin and pathological skin

Normal healthy skin has intrinsic self-repairing and self-generating faculties able to keep its structure healthy and allow the physiological life thereof.
Epidermal keratinocytes and dermal fibroblasts are the two fundamental skin cell cores having a precise biological and chronological function which maintains the ideal skin architecture. Specifically, epidermal keratinocytes (divided into two cell groups: one for regeneration and the other for maturation and keratinization only) are the cells which form the surface layer and ensure the total, continuous integrity of the skin.
In pathological situations, the skin can regenerate itself to close a wound, a loss of substance, to repair a thermal damage, etc. In these pathological cases, the skin is able to stimulate a major, specific cell regen eration process by hyper-producing keratinocytes in order to return to a normal physiological situation.

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The maturation of keratinocytes is based on the formation of keratin, which is formed by means of protein synthesis processes starting from specific amino acids, and on the formation of polyamines (spermidine, putrescine, cadaverine), by means of the urea cell cycle, with arginine acting as co-factor. In physiological conditions, the skin is regulated by a normal cellular regeneration, i.e. in given cycles: keratinocytes have a typical turnover of approximately 20 days.

Hydration of the skin

However, the skin serves other functions which typify the preservation of its physiology: specifically, the barrier function of the skin and its hydration maintenance. Although each of these skin functions is fundamental for maintaining the healthy conditions of the skin, a certain degree of structural autonomy is required for keeping the optimal physiological state: the capacity of the skin to keep an adequate hydration state is fundamental and independent from possible cell regeneration processes.
Specifically, controlling skin hydration is necessary at all ages (infants, children, adolescents, adults, elderly people) and under all skin conditions. Healthy skin and unhealthy skin, young skin and aged skin alike need to keep the right level of hydration.

Skin ageing

Specific etiological mechanisms, which determine the clinical signs of skin ageing, are present in the skin ageing processes. For an important review of the literature related to skin ageing phenomena, reference can be made to fundamental works (quoted below) such as Kligman[1], Contet-Audonneau[2], Lavker[3], Tsuji [4], Chung[5], and Garmyn[6].
The characteristics of skin ageing may be summarized in the following points:

1) Progressive thinning of the epidermis, formation of superficial and deep wrinkles, decreased cell repairing capacity and loss of skin elasticity.
2) The intricate, interconnected elastic fibre network of the dermis is decayed, and replaced by disorganised elastine deposits in the deep dermis.

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3) Reduction and disorganisation of collagen fibres with chemical and histological modifications of the cells, which determine a loss of elasticity.
4) Alteration of skin homeostasis, decreased adipose tissue layer in the hypodermis.

It is apparent that the loss of water in the dermis causes an alteration of the health status of the skin under both physiological and pathological conditions (including chrono-ageing and photo-ageing).

The invention

On the other hand, skin dryness is a very common condition in the human body, caused by endogenous and exogenous conditions (including certain environmental conditions, pollution, irritating reactions to various products, etc.), and may arise at any age.
In the scope of the instant patent, we carried out a clinical -instrumental trial for evaluating the efficacy of compounds in normal healthy skin hydration.
This trial is quoted on page 3 of European Patent Application No. 04763653.5 under "Assessment of hydration".
The invention object of European Patent Application No. 04763653.5 is based on the effect of the spermidine molecule in withholding water at the stratum corneum of the epidermis, as demonstrated by the experimental data obtained from corneometer measures.
The corneometer is an instrument for measuring stratum corneum moisture. It measures the electrical capacitance of the skin surface as an indicator of stratum corneum hydration (SCH).
The invention is based on the experimental evidence of such a trial, in which a spermidine-based composition was found to improve said degree of hydration in healthy individuals of various ages (trial carried out on individuals aged from 18 to 55 years), thus under conditions which may not be defined either as pathological or as aged skin.

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Conclusion

I do not believe that the effect of spermidine in determini ng and keeping an adequate hydration of the skin under physiological conditions, i.e. independently from the presence of a skin pathology in which the keratinocytes and the skin fibroblasts need to be modulated (by means of *up* or *down-regulation*), may at all be predictable from the prior art.

Signed by Fabio Rinaldi

Milan, 7th January 2009

BIBLIOGRAPHY

1. Kligman AM, Takase Y – Cutaneous Ageing, University of Tokyo Press, 1986; 547-555;
2. Content-Audonneau JL et al. – Br J Dermatol, 1999; 140, 1038-1047;
3. Lavker RM et al. – J Invest dermatol, 1979; 73:59-66;
4. Tsuji T et al. – British J Dermatol, 1986; 114, 329-335;
5. Chung J et al. – Photoageing, ed. Marcel Dekker, 2004; §1, 1-13;
6. Garmyn M et al. - Photoageing, ed. Marcel Dekker, 2004; § 3, 33-54

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EVALUATION OF SKIN HYDRATION AND ELASTICITY AFTER USE

1. PRODUCT

- Physical form: cream
- Colour: white

1.a. Active product FORMULA:

Composition of 100g product:

Hydrogenated polydecene	20 g
Steareth-2	3 g
Steareth-2	1 g
Cetearyl alcohol	1,5 g
diazolidinyl urea	0,3 g
Methylparaben	0,11 g
Propylparaben	0,03 g
Propylene glycol	0,56 g
Calcium pantothenate	1,9 g
Spermidine trihydrochloride	0,12 g
Biotin	0,02 g
Aqua	q.s. at 100 g

1.b. Placebo product FORMULA:

Composition of 100g product

Hydrogenated polydecene	20 g
Steareth-2	3 g
Steareth-2	1 g
Cetearyl alcohol	1,5 g
diazolidinyl urea	0,3 g

Methylparaben	0,11 g
Propylparaben	0,03 g
Propylene glycol	0,56 g
Aqua	q.s. at 100 g

2. METHOD PRINCIPLE

The purpose of the test is to establish the active ingredient efficacy for cosmetics use (Biogenina) in improving skin hydration and elasticity after a repeated use.

Twenty volunteers will use at home an emulsion containing biogenina and the respective placebo (biogenina-free emulsion) every day, twice a day, for a month. At the beginning of the test and at the end of the period of use, all the required instrumental controls relating to hydration and elasticity will be carried out.

The data generated therefrom will be then compared by an appropriate mathematical elaboration.

3. SELECTION OF VOLUNTEERS

3.a. Admission and Recruitment Criteria

At the beginning of the test, each volunteer declares that s/he has read and countersigned the informed consent drawn up by the researchers. Twenty female volunteers have been recruited.

The selection of the volunteers has been made according

to those criteria for inclusion and criteria for exclusion as referred to below.

3.b. Criteria for Inclusion

- Race: Caucasian;
- Age: 18 to 55 y.o. adults;
- Sex: female;
- Health: no pathologies during the period immediately preceding the study or in progress during the study;
- Knowledge of Italian language;
- On call at home.

3.c. Criteria for Exclusion

- Persons who do not comply with the criteria for inclusion mentioned under 4.b. above;
- Persons being under topical or systemic treatment with any drug, which may affect the results of the test;
- Pregnant or breast-feeding women;
- Persons suffering from skin diseases;
- Persons with drug and/or cosmetics intolerance background. 4A Drop-out.

3.d. Drop-out

The following reasons are considered cause of interruption of the study:

- free choice of the volunteer;
- reasons unrelated to the treatment (e.g. onset of

diseases, surgical operations, etc.);

- reasons related to the treatment (e.g. irritative, allergic reactions, etc.).

Any drop-out cases occurred during the study will be however reported.

3.e. Restrictions

Throughout the duration of the test, the volunteers will be forbidden to use, on the area under examination, cosmetics other than the one being studied (creams, lotions, etc.) and the prolonged exposure to UVA and UVB rays.